

Searching for the G₅₁₆T Polymorphism on the CYP2B6 gene in HIV-1 Patients



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Gene CYP2B6

The CYP2B6 G₅₁₆T polymorphism has a major impact on the level of hepatic metabolism.

Objectives

Identify the G₅₁₆T polymorphism located at exon 4 of the CYP2B6 gene in HIV-1 or HVC/HBV co-infected patients.

Review

The CYP2B6 gene has been mapped in the context of chromosome 19, and encodes a member of the enzyme superfamily, cytochrome P450 monooxygenase (CYP450), which is located in the endoplasmic reticulum.

This protein catalyses several reactions involved in drug metabolism.

Many genetic disorders have been reported as having influence on management, metabolism, distribution and elimination of drugs used in HIV/AIDS therapy (1).

The G₅₁₆T polymorphism in the CYP2B6 gene, present in exon 4, shows a major impact with clinical relevance on the level of hepatic metabolism, with consequently translates into changes in the respective plasmatic concentrations of drugs (2).

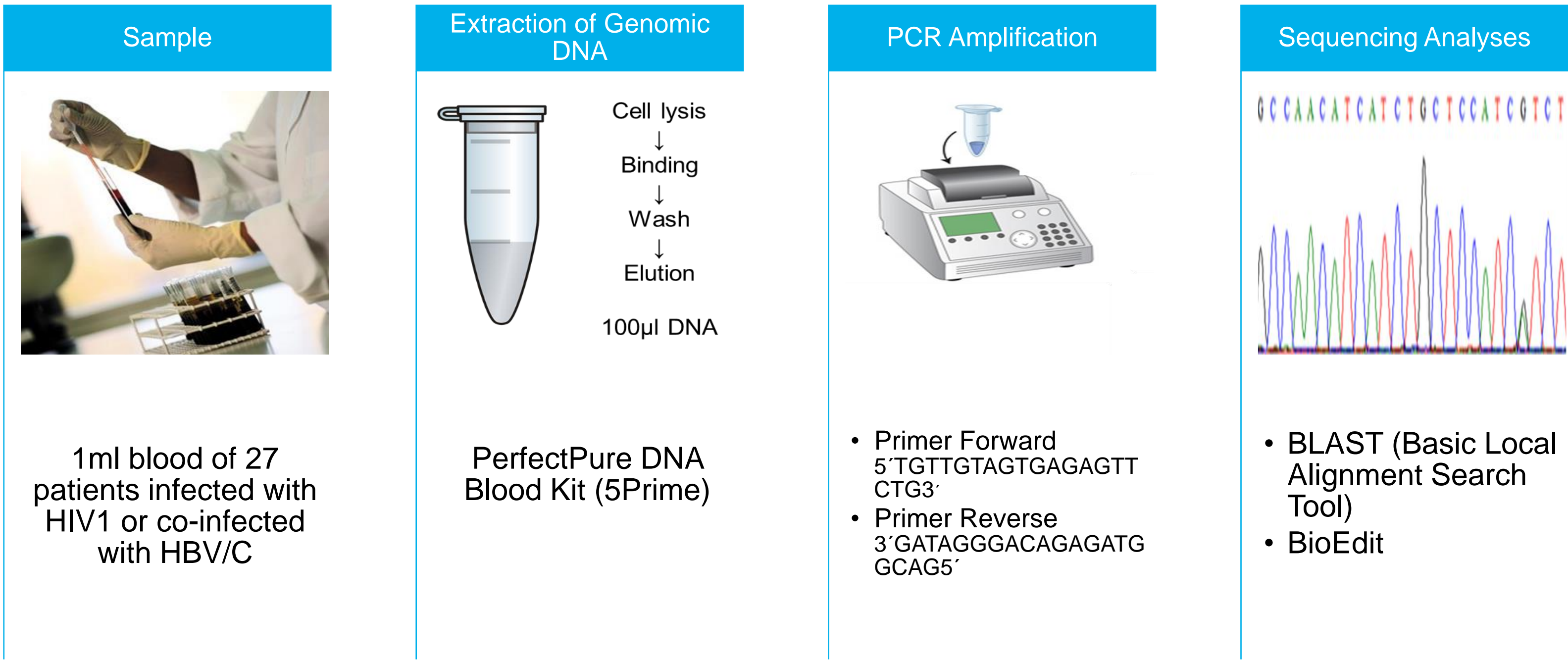
This genetic variant results in the substitution of a guanine for a thymine at nucleotide 516 of the coding sequence which leads to the amino acid substitution at position 172, glutamine for histidine (Q172H) and whose role in enzyme activity is still not clear.

This has been described as a "non-sense" polymorphism, affecting the metabolic activity by alteration of substrate binding or aberrant splicing, leading to a decreased amount of normal mRNA and thus reducing the levels of functional protein (3).

References

1. Presence of the CYP2B6 516 G>T polymorphism, increased plasma Efavirenz concentrations and early neuropsychiatric side effects in South African HIV – infected patients. Gounden *et al*, 2010. *Aids Research and Therapy*
2. Aberrant Splicing Caused by Single Nucleotide Polymorphism c.516G>T [Q172H], a Marker of CYP2B6*6, Is Responsible for Decreased Expression and Activity of CYP2B6 in Liver. Hofmann *et al*, 2008. *The Journal of Pharmacology and Experimental Therapeutics*
3. Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): advances on polymorphisms, mechanisms, and clinical relevance. Zanger and Klein, 2013. *Frontiers in Genetics*. 2013; 4: 24
4. The G516T CYP2B6 Germline Polymorphism Affects the Risk of Acute Myeloid Leukemia and is Associated with Specific Chromosomal Abnormalities. Daraki *et al*, 2014. *PLOS ONE*

Materials and Methods



Results

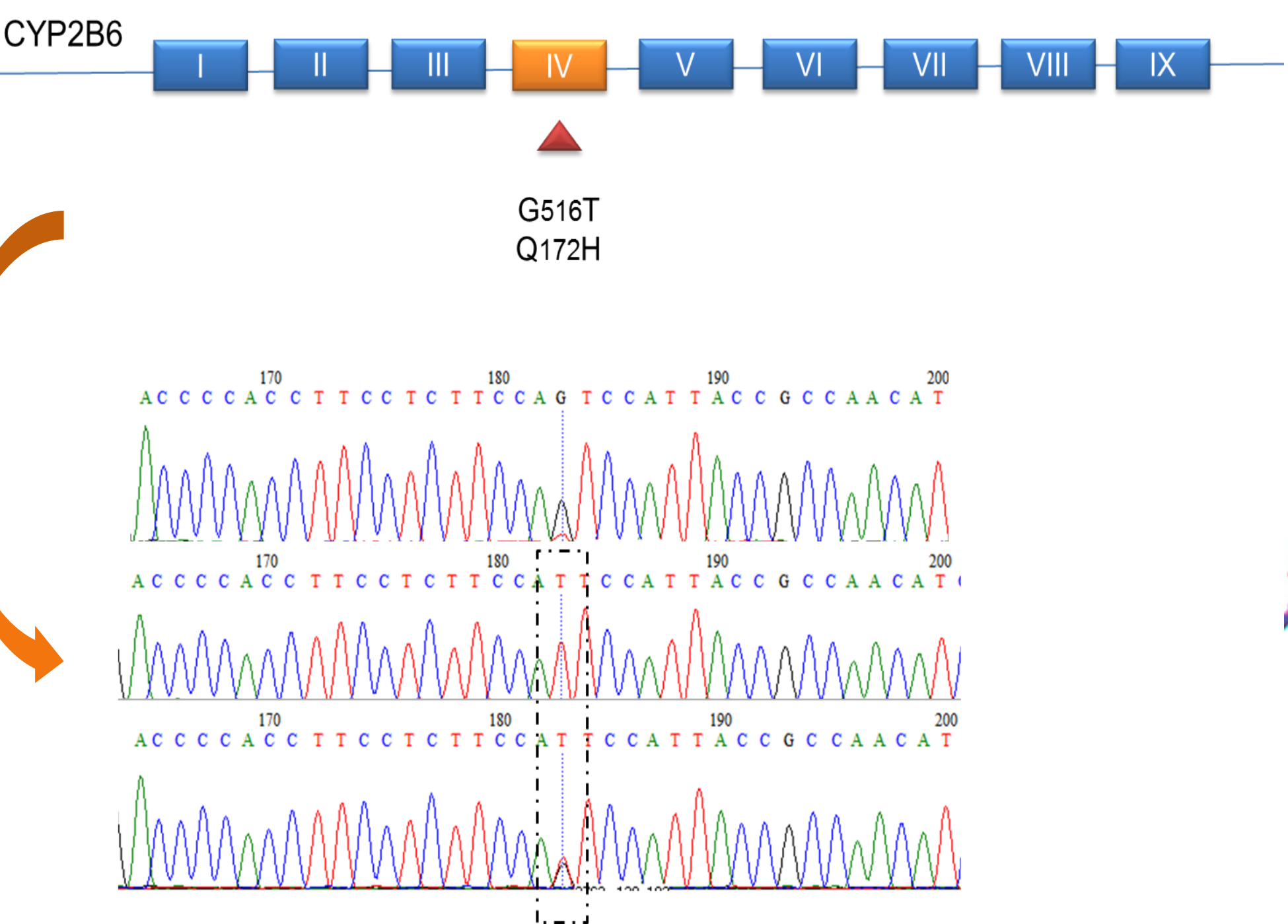


Fig. 1 - Gene CYP2B6 represented by exons and introns, the red triangle indicates the location of the SNP G₅₁₆T, the substitution leads to Glu₁₇₂His. The results of sequence alignment reveal the site of nucleotide substitution.

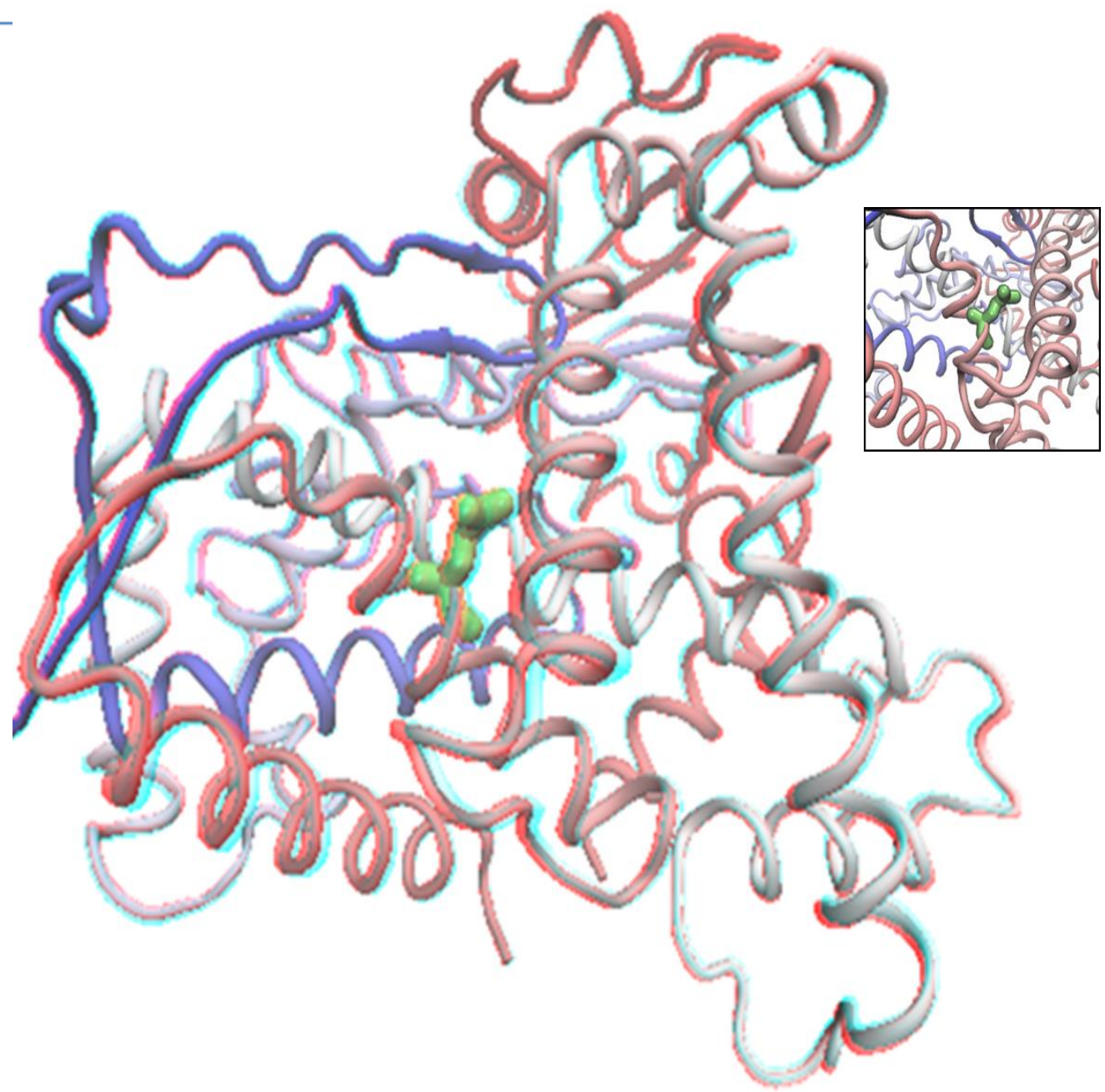


Fig. 2 - 3D structure of native CYP2B6 protein, the SNP G₅₁₆T is illustrated in green. Image acquired by VMD.

Patients	CYP2B6
	Polymorphism G ₅₁₆ T
2	G – G
8	G – T
17	T – T

25 patients present the G₅₁₆T polymorphism on the CYP2B6 gene.

Conclusion

The G₅₁₆T genetic variant can occur in heterozygosity (GT) or homozygosity (TT). Subjects with homozygous T allele (TT) exhibit enzymatic activity at lower levels when compared to individuals homozygous for the G allele (GG). Individuals heterozygous (GT) have intermediate levels (4).

Our results allow us to identify the presence of polymorphic mutation CYP2B6 G₅₁₆T in 25 patients, 8 of them carry the heterozygous genotype GT and 17 carry homozygous genotype TT.

In the future, therapeutics for HIV can be set in compliance with the patient's genetic information, leading to reduced toxicity levels and improved patient compliance to treatment.